CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MEVINPHOS

Chemical Code # 000480, Tolerance # 00157
SB 950 # 079

Revised: 5/28/87; 3/5/90; 5/25/90; 4/14/92; 6/26/92
Updated: 3/22/94

I. DATA GAP STATUS

Chronic rat :	No data gap, no adverse effect
Chronic dog :	Data gap, inadequate study, no adverse effect indicated
Onco rat :	No data gap, no adverse effect
Onco mouse :	No data gap, no adverse effect
Repro rat :	No data gap, no adverse effect
Terato rat :	No data gap, no adverse effect
Terato rabbit :	No data gap, no adverse effect
Gene mutation :	No data gap, possible adverse effect

Chromosome : No data gap, possible adverse effect

DNA damage : No data gap, possible adverse effect

Neurotox : No data gap, no adverse effect

----------**Note, Toxicology one-liners are attached**

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File Name: T940322
Revised by M. Silva, 5/25/90; J. Kishiyama & M. Silva, 3/2/92; M. Silva, 6/26/92. Updated: Kellner, 3/22/94.

Rectified with library printout (3/4/94) through volume -070, record 128430.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY SUMMARY

CHRONIC, RAT

009 034546, "Toxicity Studies on the Organophosphorous Insecticide Phosdrin: 2 Year Oral Experiment with Rats", (Tunstall Laboratory, Shell Research LTD, London, #TLRG.0043.71, October 1971). Phosdrin technical, 60.2% cis-isomer, 39/sex, fed in the diet at 0, 0.5, 1.5, 5.0, and 15.0 ppm; negative control had 78/sex; mean dietary concentrations were calculated to be 74.25% of nominal; interim sacrifices at 6, 12, and 18 months; males 42-58% mortality and females 54-71% - not dose related; no adverse effect noted; UNACCEPTABLE, incomplete, data presented in summary form only; inadequacies exist in individual animal data, dose justification, ophthalmology, hematology, urinalysis and histopathology, not upgradeable. (Shimer, Apostolou 9/23/85, Martz 11/30/86)

006 020019. Summary of 034546 in 009

010 and 013 048723, rebuttal/response to CDFA review of 034546 in 009, (no status change). (Martz 11/30/86)

COMBINED CHRONIC/ONCO, RAT

**068 127978 Plutnick, R. "2-Year Chronic Toxicity/Oncogenicity Study in Rats with Mevinphos (MRD-88-331)" (Exxon Biomedical Sciences, Inc., Toxicology Laboratory, East Millstone, N.J., Study #233170C, 1/3/94). Mevinphos technical (purity 85.74%, lot #910072) was administered by oral gavage 5 days/week to 80 Sprague-Dawley Crl:CDBR rats (30/sex/dose 1-year chronic and 50/sex/dose 2-year oncogenicity) at levels of 0, 0.025, 0.35, 0.60/0.70 mg/kg/day (dose lowered in females on day 83 due to overt toxicity); compound-related increase in mortality in high-dose males, apparently due to acute toxicity (ChE inhibition effects), was seen by

study termination. Clinical signs immediately after dosing included tremors and exophthalmus. **NOEL (for cholinergic signs) = 0.025 mg/kg/day.** High-dose males (chronic; 1-year sampling) had cholinesterase (ChE) activity in plasma, RBC and brain that was 57%, 6% and 53% lower than control, respectively; corresponding females showed reductions of 71%, 8% and 55%, respectively (significant reductions also seen in 0.35 mg/kg/day rats). **ChE NOEL = 0.025 mg/kg/day.** No significant effects on body weight or organ weights; no significant non-neoplastic findings during gross necropsy or histopathologic examinations. **No Adverse Chronic Effects** (no non-ChE related findings at the highest dose tested). Although increased liver adenomas in high-dose males and increased in combined liver adenomas and carcinomas in females achieved statistical significance, the percentages of animals involved were small and the changes were not indicative of a compound-related effect. **No Adverse Oncogenic Effects.** ACCEPTABLE. Kellner, Aldous and Gee, 3/18/94.

051 112087 "Two Year Chronic Toxicity/Oncogenicity Study in Rats (MRD-88-331; Mevinphos," (Interim Report to -068:127978). No Worksheet. M. Silva, 4/14/92.

SUBCHRONIC, RAT

057 119598 "90-Day Subchronic Oral Toxicity Study in Rats with Mevinphos (MRD-88-331): 233170B", (R.T. Keefe, EXXON Biomedical Sciences, Inc., 11/4/92). Mevinphos, purity 89.57% (74.48% α isomer and 15.09% β isomer), was administered by oral gavage to 10 male Crl:CDBR Sprague-Dawley (SD) rats/group at 0, 0.05, 0.50, 1.0, or 1.5 mg/kg/day and 10 females/group at 0, 0.01, 0.05, 0.5 or 0.75 mg/kg for 90 days. Mortality: 5 males in each of the two high-dose groups resulted in reduction of dosage from 1.5 to 1.0 mg/kg at day 36; one female in 0.5 mg/kg group died. Clinical signs included pinpoint pupils in all but the low dose male group and also tremors, oral discharge and ocular discharge in the two highest dose groups. Cholinesterase (ChE) inhibition (plasma and brain) was observed at doses above 0.05 mg/kg. Liver toxicity was indicated with a trend toward increased liver weights (two highest dose male and female) and hepatocellular vacuolation of centrilobular and midzonal hepatocytes in 2 high-dose males. NOEL = 0.05 mg/kg/day (for ChE inhibition and systemic toxicity). These data support the dose levels administered in the 2-year chronic/onco study (-068:127978). No worksheet is needed, since the study did not identify unique toxicological concerns, nor did it show a lower NOEL than the 2-year study. Data were examined by Kishiyama and Kellner, 3/22/94.

CHRONIC, DOG

062 123702 Protocol for "A 52-Week Oral (Capsule) Toxicity Study of Mevinphos in the Beagle Dog" Amvac Chemical Corporation. This submission is the protocol for a 1-year dog chronic study that was scheduled to begin 7/6/93 (final report to be ready by 3/1/95). The sponsor was originally going to proceed with a 90-day dog study prior to the 1-year dog study because of problems with emesis and attaining an MTD. Instead, a preliminary study (single male dog) using a modified feeding/dosing regimen revealed that a dose level of 0.5 mg/kg could be tolerated for 6 consecutive days. Based on this result, Amvac decided to proceed directly to the 1-year study; this study is now in progress. Preliminary data from the first 3 months and during weeks 13 through 26 were submitted in -064:126501 and -070:128430, respectively. No Worksheet. Kellner, 3/21/94.

064 126501 Preliminary report (covering day 0 to 3rd month) for "A 52-Week Oral (Capsule) Toxicity Study of Mevinphos in the Beagle Dog" Amvac Chemical Corp. project #85746. Kangas, L. (9/30/93). The author reported compound-related effects on RBC and plasma cholinesterase (ChE) levels at 4 and 12 weeks. Males at 12 weeks had mean RBC ChE levels of 105%, 112%, 89% and 68% of pretreatment values in the 0, 0.025, 0.25 and 0.50 mg/kg/day groups, respectively. Corresponding female values were 78%, 109%, 55% and 34%, respectively. For male plasma ChE, these values were 103%, 86%, 50% and 36%, and for females they were 99%, 88%, 53% and 43% of the pretreatment levels, respectively. No other compound-related effects were reported; clinical signs consisting of soft feces and emesis were considered incidental. No Worksheet. Kellner, 3/21/94.

070 128430 Preliminary report (covering weeks 13 to 26) for "A 52-Week Oral (Capsule) Toxicity Study of Mevinphos in the Beagle Dog" Amvac Chemical Corp. project #85746. Kangas, L. (1/14/94). The author reported significant ChE inhibition in RBC and plasma in mid- and high-dose animals. Low-dose males also showed significant reductions in ChE activity. Clinical signs consisted of slightly higher incidence of emesis in the high-dose animals, therefore the apparent NOEL (excluding ChE enzyme inhibition) is 0.25 mg/kg/day. Soft feces were seen in all groups (i.e., this was considered an incidental finding). No other compound-related effects were reported. No Worksheet. Kellner, 3/21/94.

045 092717, "Range-Finding Study of Mevinphos Administered Orally to Beagle Dogs (Preliminary Study #1)," (V. Reddy, D.W. Arneson, B.W. Maidment, Midwest Research Institute, MRI Project No. 9497-F, 3/26/91). Mevinphos technical (purity = 89.57%) was administered orally in capsules at concentrations of 0 (corn oil), 0.025, 0.05, 0.25 (elevated to 1.0 mg/kg on day 14 of dosing), or 0.50 mg/kg to 2 Beagle dogs/sex/group for three weeks. NOEL = 0.025 (Decreased plasma cholinesterase values of $\geq$ 45% in both sexes at $\geq$ 0.25 mg/kg. Vomiting occurred in both sexes at $\geq$ 0.05 mg/kg. Motor activity decreased at $\geq$ 0.5 mg/kg). These data are supplemental. (Kishiyama & Silva, 1/31/92).

045 092716, "Range-Finding Study of Mevinphos Administered Orally to Beagle Dogs (Preliminary Study #2)," (V. Reddy, D.W. Arneson, B.W. Maidment, Midwest Research

Institute, MRI Project No. 9497-F, 3/26/91). This study was initiated to test a split dosing system to reduce emesis and to test specific areas of the brain for cholinesterase activity. Mevinphos technical (89.57% pure) was administered orally in capsules at concentrations of 0 (corn oil) or 0.5 mg/kg/day to 1 Beagle dog/sex/group once daily and to another like set but dosed twice daily (0 and 1.0 mg/kg total/animal/day) for 5 days. Vomiting seemed to be somewhat related to the amount of treatments. Appetite (food consumption) and weight were affected in the twice treated group. Cholinesterase was not significantly affected by mevinphos. (Kishiyama & Silva, 2/5/92).

009 034547, "Toxicology Studies on the Organophosphorous Insecticide Phosdrin, Two Year Oral Dosing Experiment with Dogs", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0052.71, December 1971). Phosdrin technical, 60.2% cis-isomer, at 0, 0.025, 0.075, 0.25, and 0.75 mg/kg in gelatin capsules in olive oil, 4/sex/group, no consistent dose related effects observed; no adverse effect noted; apparent NOEL 0.025 mg/kg/day (CHE inhibition); UNACCEPTABLE, incomplete; deficiencies include dose level justification, hematology, urinalysis, ophthalmology, individual animal data, and histopathology; not upgradeable. (Shimer, Apostolou 9/23/85, Martz 11/30/86).

006 020018. Summary of 034547 in 009

010 and 013 048724, rebuttal/response to DPR review of 34547 in 009, (no status change). (Martz 11/30/86).

ONCOGENICITY, RAT

See Combined Chronic/Onco Rat (-068:127978)

ONCOGENICITY, MOUSE

** 028 073163, "An Eighteen Month Oncogenicity Feeding Study in Mice with Mevinphos", (Bio/dynamics Inc., Project no. 86-3006, 2/23/89). Mevinphos technical (purity = 100%) mixed in the feed at concentrations of 0 (diet only), 1, 10, or 25 ppm were fed to 50 CD-1 mice/sex/group for approximately 18 months. No adverse effect. NOEL = 10 ppm (transient decrease in body weights for both sexes). NOAEL $\geq$ 25 ppm. Cholinesterase inhibition was not measured. Dose selection was based on a 3 month study. ACCEPTABLE. (Kishiyama & Silva, 3/1/90).

REPRODUCTION, RAT

** 050 111291 "Multi-Generation Rat Reproduction Study MRD-88-331: Mevinphos," (Beyer, B.K., Exxon Biomedical Sciences, Inc., ID#: 233135, 11/26/91). Mevinphos technical was administered via oral intubation (7 days/week) to Crl:CD BR VAF/Plus Sprague-Dawley rats (35/sex/group) at 0 (reverse osmosis water), 0.05, 0.1 and 0.5 mg/kg for 2 generations (1 litter/generation). Reproduction NOEL = 0.1 mg/kg (There were decreased numbers of corpora lutea in P2 dams at 0.5 mg/kg.) Chronic NOEL = 0.1 mg/kg (P1 females at 0.5 mg/kg showed ataxia, coarse and fine tremors, oral discharge and pinpoint pupils. There was a significant decrease in ovaries/body weight at 0.5 mg/kg.) Pup NOEL = 0.1 mg/kg (There was a significant decrease in mean pup weights on day 21, survival indices for days 1, 4 and 14 and the lactation index in the P1 generation. There was a significant decrease in male pup weights on day 21 and in day 4 survival index in the P2 generation.) Cholinesterase NOEL = 0.1 mg/kg (Plasma (44-60%) and brain (41-51%) cholinesterase were inhibited at 0.5 mg/kg in both sexes for both generations.) No adverse effect. The study is acceptable. M. Silva, 2/20/92.

NOTE: A disclosure statement for possible adverse effects was submitted by the registrant (January 18, 1991) in reference to results observed in a range-finding study (no record #, ID # SBC-126884-E). In light of the results of the definitive rat reproduction study (no adverse effects), this document does not need to be further addressed (no worksheet). M. Silva, 2/20/92.

009 034549, "3-Generation Reproduction Study of Phosdrin Insecticide in Rats", (Hill Top Research, Inc., Miamiville, Ohio, #P-5, 10/24/67). Phosdrin Insecticide, 60% alpha isomer and 40% related compounds; at 0, 1.2, and 24 ppm in Purina Lab Chow to 10 males/group and 2 females/group for 3-generations, 2 litters/generation; no adverse reproductive effect reported; NOEL ≥ 24 ppm (nominal), UNACCEPTABLE, incomplete; lack of toxicity at high dose, poor pup survival in F2b control and treated groups; does not include analysis of diet, dose level justification, and complete histopathology data; not upgradeable. (Shimer, Parker 9/24/85, Martz 11/30/86).

006 955232. Summary of 034549 in 009.

010 and 013 048726, rebuttal/response to DPR review of 034549 in 009 (no status change). (Martz 11/30/86).

TERATOLOGY, RAT

**016 055833, "Mevinphos - A Teratology Study in Rats with Mevinphos", (Bio/dynamics Inc., 85-3009, March 2, 1987). Mevinphos technical, lot 50826, 12/18/85, administered by gavage in distilled water to groups of 24 mated Sprague-Dawley rats at levels of 0, 0.2, 0.75, and 1.00 mg/kg on days 6 - 15 of gestation. The initial high dose group, 1.25 mg/kg/day was terminated due to excessive maternal toxicity (tremors and salivation) was observed at 0.75 and 1.00 mg/kg/day, Maternal NOEL = 0.2 mg/kg/day. There was no evidence of developmental toxicity at any dose level, Developmental NOEL > 1.00 mg/kg/day. ACCEPTABLE, no adverse effect. (J. Parker, 4-28-87)

015 055832. Range finding study for 055833.

TERATOLOGY, RABBIT

** 042 096691, "Teratology Study in Rabbits (MRD-88-331: Mevinphos)", (B. K. Beyer, Exxon Biomedical Sciences Inc., Laboratory Project I.D. 233134RB, 2/22/91). Mevinphos (89.57% pure), administered by oral gavage at concentrations of 0, 0.05, 0.5 and 1.5 mg/kg/day to artificially inseminated New Zealand White rabbits (20/group) on days 7 through 19 of gestation. **Maternal NOEL =** 0.5 mg/kg (There was a significant decrease in body weight gain at 1.5 mg/kg.) **ChE NOEL =** 0.05 mg/kg (There was a significant decrease in plasma and RBC ChE at ≥ 0.5 mg/kg.) **Developmental NOEL =** 1.5 mg/kg (No significant effects were observed at any dose level.) Maternal body weight gains were decreased, but no other toxic effects were observed. Decreases in plasma and RBC cholinesterase were measured without cholinergic signs. Although there was little evidence of maternal toxicity, the dose selection for this study was justified, based upon the pilot. Originally reviewed as unacceptable (Silva, 2/6/92). Upon submission and review of stability data, recomputed data from Table 3, historical control data for fetal malformations and variations and information on pregnancy status of animal HEB054, the study has been upgraded to acceptable status, with no adverse effect indicated. In addition, the cholinesterase data were re-examined and the NOEL was adjusted to 0.05 mg/kg, based on plasma ChE inhibition. M. Silva, 6/17/92.

009 034548 "Toxicity Studies With Phosdrin: Teratological Studies in Rabbits Given Phosdrin Orally," (Dix, K.M. and McCarthy, W.V., Tunstall Laboratory and the Statistics Unit of Sittingbourne Research Centre, Shell Research LTD, London, #TLGR.0016.74, 4/74). Phosdrin (purity = 71.6%/17.1% 2-methoxycarbonyl-1-methylvinyl dimethyl phosphate in E/Z forms; batch #ADC/73/5) was administered in gelatin capsules to mated Dutch rabbits (30--control and 20/dose group) at 0 (corn oil), 0.3 and 1.0 mg/kg/day during days 6-18 of gestation. Maternal NOEL = 0.3 mg/kg (7/20 rabbits at 1.0 mg/kg exhibited occasional mild tremors, salivation and signs of organophosphate toxicity, shortly after dosing--no summary table, no individual data). **Developmental NOEL** ≥ 1.0 mg/kg (No significant teratogenic effects were reported at any dose.) This study is not acceptable and not upgradeable (deficiencies are too numerous to list in the one-liner). A. Apostolou (9/23/85), F. Martz (11/30/86) and M. Silva, (3/25/92).

006 020017. Summary of 034548 in 009.

010 and 013 048725, rebuttal/response to CDFA review of 034548 in 009; possible status change, study may be acceptable/upgradeable if more information is supplied. (Martz, 11/86).

MUTAGENICITY, GNMU

** **034 085454**, "CHO/HGPRT Mutation Assay with Confirmation with Mevinphos", (Microbiological Associates Inc., Laboratory Study No. T8858.332001, 11/9/89). Mevinphos (purity = 74.48% alpha isomer and 15.09% beta isomer) was tested with Chinese Hamster ovary cells (CHO-K_1-BH_4) at concentrations of 0.1, 0.4, 0.6, 0.8, 1.0 µl/ml without S-9 activation and at 0.1, 0.6, 1.2, 1.8, or 2.4 with Arochlor-induced rat liver S-9 (exposure = 5 hours) in an initial study. In another study the cells were tested with mevinphos at 0.5, 0.6, 0.7, 0.8, 0.9, or 1.1 without S-9 and 0.6, 0.9, 1.2, 1.4, 1.6, or 1.8 µl/ml with S-9 in a repeat assay. **Adverse effect** (the number of mutant/10^6 clonable cells, without S-9 increased at 1.0 µl/ml in the initial test and at 0.9 µl/ml in the repeat test). Relative cloning efficiency averaged 16-20% and 42% for mevinphos doses at 1.0 and 0.9 µl/ml, respectively. ACCEPTABLE. (Kishiyama & Silva, 2/26/90).

** **030 087669**, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with A Confirmatory Assay with Mevinphos", (Microbiological Associates, Inc., Laboratory study No. T8858.501014, 10/23/89). Mevinphos (purity = 74.48% alpha isomer, 15.09% beta isomer) was used at concentrations of 0 (deionized water), 100, 1000, 3333, 6667 or 10000 µg/plate exposures to Σαλμονελλα τψπηιμυριυμ strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation (S-9 Mix) for 48 hours. **Adverse effect.** An increase in TA100 revertant colonies was observed at ≥ 3333 ug/plate both with and without S-9. ACCEPTABLE. (Kishiyama & Silva, 2/28/90).

009 034551, "The Mutagenic Effect of Organophosphate Insecticides on Escherichia coli", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0034.71, August, 1971). Phosdrin, 67.3% W cis-isomer, plate incorporation assay with E. coli B/r WP2 in triplicate seeded at

9x108/plate; no reverse mutation reported; UNACCEPTABLE, incomplete, summary information only; no data - results as "-" only, lacks dose level selection and justification and control information. (Green, Parker 5/13/87).

006 035764. Summary of 034551 in 009.

MUTAGENICITY, CHROMOSOME

** **035, 036 090374, 086427** "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells With Mevinphos," (Microbiological Associates, Inc., 1/18/90). Mevinphos technical (purity = 76% alpha isomer; 13.5% beta isomer) was used in a chromosome aberration assay using Chinese hamster ovary cells at 0 (vehicle = culture medium or water), 0.04, 0.08, 0.15, 0.3 and 0.6 ul/ml (without S-9; 18 hour treatment in duplicate) and 0.13, 0.5, 1.0 and 2.0 ul/ml (with S-9; 2 hour treatment in duplicate). A repeat assay was performed without S-9 at 0.15, 0.21, 0.30 and 0.42 ul/ml Mevinphos. **Possible adverse effect.** The percentage of Mevinphos treated cells (no S-9) with chromosome aberrations was significantly increased over the controls at ≥ 0.15 ul/ml. This worksheet was revised with the addition of CDFA volume/record #: 036/086427 which contains an analysis of technical Mevinphos (no separate worksheet). ACCEPTABLE. M. Silva, 5/18/90.

009 034550, "Toxicity Studies with Phosdrin: Dominant Lethal Assay in Male Mice after a Single Oral Dose of Phosdrin", (Tunstall Laboratory, Shell Research LTD, London #TLGR.0031.74, July, 1974). Phosdrin, methyl 3-(dimethoxy phosphinyloxy) crotonate, E-isomer 70.0%, batch no. ACD 73/69; single oral dose in water at 0, 1.5, 3.0, and 6.0 mg/kg to males 12/group, mated 1 male/3 females/week for 8 weeks; females sacrificed 13 days after mating; no dominant lethal effects reported; no adverse effect noted; UNACCEPTABLE, not upgradeable; deficiencies include no MTD, no concurrent historical or positive control, and no individual data. (Shimer, Remsen 9/25/85).

006 035763. Summary, insufficient information for evaluation.

006 955233. Summary of 034550 in 009.

010 and 013 048727, rebuttal/response to CDFA review of 034550 in 009, (no status change). (Martz 11/30/86).

009 034555, "Toxicity Studies with Phosdrin: Chromosome Studies on Bone Marrow Cells of Mice after Two Daily Oral Doses of Phosdrin", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0008.74, February 1974). Phosdrin E-isomer 70.0%, batch no. ACD 73/69 dosed twice orally on 2 consecutive days in water 8/sex/group at 0, 1.5, and 3.0 mg/kg, positive control of 100 mg/kg cyclophosphamide; colcemid 90 minutes prior to sacrifice, sacrificed at 8 and 24 hours after dosing 100 cells/animal; no bone marrow chromosomal aberration reported; UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

010 and 013 048728, rebuttal/response to CDFA review of 034555 in 009, (no status change). (Martz 11/30/86).

MUTAGENICITY, DNA

** 035, 036 090373, 086427 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes With Mevinphos," (Microbiological Associates, Inc., 1/25/90; Study #: T8858.380). Mevinphos technical (purity = 76.34% alpha isomer; 13.5% beta isomer) was used in a UDS assay on primary rat (Fischer 344 or Sprague-Dawley) hepatocytes at 0 (vehicle = William’s Medium E), 0.0003, 0.001, 0.003, 0.01, 0.03, 0.06, 0.1, and 0.3 ul/ml for 18-20 hours (3 plates/dose + [3-H]Thymidine at 10 uCi/ml/plate). A parallel cytotoxicity test was also performed (3 plates/dose). After treatment, cells were placed on coverslips and slides were prepared (50 cells/slide were scored; 3 slides/dose). No adverse effect. No increase in UDS was observed at any dose. This worksheet was revised with the addition of CDFA volume/record #: 036/086427 which contains an analysis of technical Mevinphos (no separate worksheet). ACCEPTABLE. Volume 036/086427 contains an analysis of Mevinphos technical. M. Silva, 5/18/90.

009 034552, "Toxicity Studies with Phosdrin: Effect of Phosdrin on Micro-Organisms in the Host-Mediated Assay and in vitro", (Tunstall Laboratory, Shell Research LTD London, #TLGR.0067.74, November 1974). Technical Phosdrin, 81.9% E-isomer of methyl 3-(dimethoxyphosphinoxy) crotonate; spot test on plates with Serratia marcescens; NTG as positive control; no reversion reported; no data, summary only; UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

009 034553, "Toxicity Studies with Phosdrin: Effect of Phosdrin on Micro-Organisms in the Host-Mediated Assay and in vitro", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0067.74, November 1974). Technical Phosdrin, 81.9% E-isomer of methyl 3-(dimethoxyphosphinoxy) crotonate, in vitro study in triplicate with Saccharomyces cerevisiae at 0, 0.2, 1, 2, and 4 mg/ml NTG positive control; at 1 mg/ml increase in conversion rate at adenine locus after 24 hour incubation; summary data only; **possible adverse effect** (genotoxicity); UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

009 034554, "Toxicity Studies with Phosdrin: Effect of Phosdrin on Micro-Organisms in the Host-Mediated Assay and in vitro", (Tunstall Laboratory, Shell Research LTD, London, #TLGR0067.74, November 1974). Technical Phosdrin 81.9% E-isomer of methyl 3-(dimethoxyphosphinoxy) crotonate, host-mediated assay in triplicate, male CF-1 dosed orally at 0, 1.5, and 3.0 mg/kg, EMS positive control; Saccharomyces cerevisiae D4 injected; sacrificed at 5 hours; tryptophan and adenine plate assay, no positive effects reported; no adverse effect noted; summary data only, UNACCEPTABLE, not upgradeable. (Shimer, Remsen 9/25/85).

006 035762. Summary of 034552, 034553, and 034554 in 009.

NEUROTOXICITY, HEN

010 048729. Rebuttal to 034556, in 009, status change: report acceptable with major deficiencies.

** 053 114192 "Acute Delayed Neurotoxicity Study in Mature Hens With Mevinphos," (Barrett, D.S., Bio/dynamics Inc., Department of Toxicology, East Millstone, NJ, 7/26/88). Mevinphos technical (no purity given, batch #50826) was administered by gastric intubation to White Leghorn pullet hens at 0 (distilled water, 6 hens), 12.5 mg/kg (10 hens) and positive control animals were given TOCP at 750 mg/kg (4 hens) on days 0 and 21 of the study. Mevinphos treated animals received 5-17 s.c. injections of Atropine (0.625 mg/kg) during the 48 hours after dosing. An injection of 2-PAM (10 mg/kg/injection) was administered s.c. at approximately 5 & 11 hours after the 2nd dose of mevinphos. The positive control was TOCP (750 mg/kg). NOEL Delayed Neurotoxicity > 12.5 mg/kg (No significant neurotoxic effects occurred at the given dose.) No adverse effect. Acceptable. M. Silva, 6/23/92.

**009 034556, "Toxicity Studies on the Organophosphorus Insecticide Phosdrin: An Investigation of the Potential Neurotoxicity of Technical Phosdrin", (Tunstall Laboratory, Shell Research LTD, London, #TLGR.0047.72, November, 1972). Technical Phosdrin (purity 60.2% cis-isomer), 0 or 7.5 mg/kg (~LD50) by oral gavage once on day 1 and 23 with sacrifice on day 43, TOCP positive control, atropine and protopam protection; no clinical signs of delayed neurotoxicity in phosdrin group; 3/6 phosdrin hens died after second dose; 1 dead and 3 survivors examined histologically no evidence of delayed neurotoxicity found. Previously reviewed (AA, 9/23/85) unacceptable and not upgradeable. Rebuttal accepted, repeat of study would not provide additional information. Report ACCEPTABLE with major deficiencies. (F. Martz, 12/2/86).

NEUROTOXICITY, RAT

066 126747 Lamb, I. "An Acute Neurotoxicity Study of Mevinphos in Rats" (WIL Research Laboratories, Inc., Ashland, Ohio; WIL Study # 188006, 10/13/93). Mevinphos technical (lot # 910072, 86.55% purity) was administered in a single oral dose to 27 Sprague-Dawley Crl:CD* BR rats/sex/dose (except for the 0.025 mg/kg group which had 17/sex) at levels of 0, 0.025, 0.1, 2.0 and 3.5 mg/kg. Compound related deaths included 1 male and 5 females (3.5 mg/kg); no body weight effects were noted. Clinical signs (45-min. after dosage) in the 2.0 and 3.5 mg/kg

groups included gait alteration, tremors, salivation, exophthalmus and lacrimation. Plasma cholinesterase (ChE) reductions ranged from 36-39% of control in the 2.0 mg/kg group and 41-50% in the 3.5 mg/kg group. Brain ChE (brain stem and/or cerebral cortex, hippocampus and olfactory region) ranged from 20-25% of control in the 2.0 mg/kg group and from 19-36% in the 3.5 mg/kg group; no appreciable RBC ChE reductions were reported. **Possible Adverse Effects:** For Functional Observation Battery (FOB) during day 0, home cage observations included altered posture, clonic convulsions and tremors primarily in the high-dose rats. Handling observations (FOB): lacrimation, salivation, decreased respiratory rate (and/or gasping), red deposits (nose and mouth) and changes in eye prominence. Open field observations: impaired mobility and gait, clonic and tonic convulsions, tremors, bizarre and/or stereotypic behavior, decreased arousal and decreased rearing counts. Sensory observations: air righting reflex (and approach), touch, startle, tail pinch, pupil and eyeblink reponses. Neuromuscular observations: reduced hindlimb resistance and forelimb grip strength rotarod performance. Physiological observations: increased catalepsy values and decreased body temperatures; no significant findings during subsequent FOB observations. Reductions in mean ambulatory and total motor activity were noted on Day 0 in the 2.0 and 3.5 mg/kg dosage groups. NOEL = 0.1 mg/kg for ChE inhibition and neurobehavioral effects. ACCEPTABLE. Kellner and Gee, 2/15/94.

065 126746 Lamb, I. "A Range-Finding Acute Study of Mevinphos in Rats" (WIL Research Laboratories, Inc., Ashland, Ohio; WIL Study # 188005, 10/12/93) was a range-finding study for the acute neurotoxicity study -066:126747. The data support the dose range used. No Worksheet. Kellner, 3/21/94.

SUPPLEMENTAL STUDIES

053 114188 "21-Day Repeated Dermal Study in the Rabbit," (Trimmer, G.W., Exxon Biomedical Sciences, Inc., NJ, 4/4/90, MRD-88-331). Mevinphos technical (89.57% pure, Batch #1) was administered to New Zealand White rabbits (5/sex/dose) on clipped unabraded skin (5 days/week for 3 weeks--6 hr exposure) at 0, 0.1, 1.0 and 10.0 mg/kg. Cholinesterase determinations were performed on all animals (RBC, plasma and brain). Dermal NOEL > 10.0 mg/kg (No effects at any

dose.) ChE NOEL = 1.0 mg/kg (Plasma, RBC and brain cholinesterase levels were significantly inhibited at 10.0 mg/kg). Possible adverse effect: Significant inhibition of brain cholinesterase. M. Silva, 6/17/92.